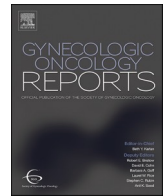


# **Exhibit 77**



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## Review article

## Etiopathogenesis of ovarian cancer. An inflamm-aging entity?

Manuel Sánchez-Prieto<sup>a,\*</sup>, Rafael Sánchez-Borrego<sup>b</sup>, Daniel Maria Lubián-López<sup>c</sup>,  
Faustino R. Pérez-López<sup>d</sup><sup>a</sup> Department of Obstetrics and Gynecology, Instituto Universitario Dexeus, Barcelona, Spain<sup>b</sup> DIATROS, Clínica de Atención a la Mujer, Barcelona, Spain<sup>c</sup> Department of Obstetrics and Gynecology, University Hospital of Jerez de la Frontera, Cádiz, Spain<sup>d</sup> Department of Obstetrics and Gynecology, University of Zaragoza, Zaragoza, Spain

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## ABSTRACT

Ovarian cancer is one of the most common gynecologic cancers and has the highest mortality rate. The risk/protective factors of ovarian cancer suggest that its etiology is multifactorial. Several factors are involved in age-related increases in carcinogenesis, including the accumulation of senescent cells, inflammaging (a chronic inflammatory state that persists in the elderly), and immunosenescence (aging of the immune system) changes associated with poor immune surveillance. At sites of inflammation, exposure to high levels of inflammatory mediators, such as reactive oxygen species, cytokines, prostaglandins, and growth factors, contributes to increased cell division and genetic and epigenetic changes. These exposure-induced changes promote excessive cell proliferation, increased survival, malignant transformation, and cancer development. Furthermore, the proinflammatory tumor microenvironment contributes to ovarian cancer metastasis and chemoresistance.

This narrative review of the literature was carried out to delineate the possible role of inflammaging in the etiopathogenesis of ovarian cancer development. We discuss the current carcinogenic hypotheses, sites of origin, and etiological factors of ovarian cancer. Treatment of inflammation may represent an attractive strategy for both the prevention and therapy of ovarian cancer.

## 1. Introduction

Ovarian cancer (OvCa) is the second most common gynecological cancer in the United States and Western Europe (Khazaei et al., 2021); it causes more deaths than all other gynecological cancers combined (Menon et al., 2021). Therefore, prevention strategies are being established to reduce the risk of OvCa (Pérez-López et al., 2017). Such strategies include opportunistic salpingectomy, which is the most effective intervention (Hanley et al., 2022); genetic testing for individuals who are at high risk, risk reducing surgery for individuals with inherited genetic testing, effective clinical management of endometriosis, policies to prevent the onset of tobacco use and promote smoking cessation (Yarmolinsky et al., 2019), and the use of most contraceptive methods (Sánchez-Borrego and Sánchez-Prieto, 2021).

The incidence of OvCa increases with age and reaches its peak in the seventh decade of life (Momenimovahed et al., 2019). Aging leads to numerous changes that affect many components of the immune system, called “immunosenescence” (Lian et al., 2020). Immunosenescence is a

process of immune dysfunction that occurs with age and includes remodeling of lymphoid organs, leading to changes in the immune function of the elderly, which is closely related to the development of infections, autoimmune diseases, and malignant tumors (Lian et al., 2020). Indeed, elderly individuals exhibit increased susceptibility to many diseases, including cancer, autoimmune disorders, and other chronic inflammatory diseases (Feehan et al., 2021).

Inflammation has been considered a key mechanism for carcinogenesis after detecting leukocytes in cancer tissues. Inflammation can mediate and stimulate the production of tumor-promoting compounds, including cytokines, especially interleukin (IL) 6 and 8 and chemokines, as well as reactive oxygen species (ROS), tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$ , and lipid hydroperoxides (Browning et al., 2018). These compounds can contribute to cell proliferation, malignant transformation, and cancer development (Savant et al., 2018; Zhou et al., 2021; Crusz and Balkwill, 2015).

Among other factors, such as hereditary, environmental, and lifestyle factors, inflammation is an important risk factor for OvCa. Several

\* Corresponding author at: Instituto Universitario Dexeus, Sabino de Arana 5-19, 08028 Barcelona, Spain.

E-mail address: [mansan@dexeus.com](mailto:mansan@dexeus.com) (M. Sánchez-Prieto).

studies have suggested that factors related to ovarian surface epithelium (OSE) inflammation, such as ovulation, endometriosis, and pelvic inflammatory diseases (PIDs), are associated with an increased risk of OvCa (Trabert et al., 2020; Tanha et al., 2021). Mucin 16 (MUC16) is a membrane-associated gene that encodes cancer antigen 125 (CA125), and the upregulation of its expression is another mechanism underlying the effects of inflammatory factors in OvCa (Liu et al., 2021). The inflammation-associated factors lipopolysaccharides, IL-6, IL-8 and TNF- $\alpha$  increase the expression levels of MUC16 and enhanced CA125 release in OvCa (Liu et al., 2021).

The term “inflammaging” is used to define the systemic and sterile (in the absence of infection) low-grade chronic inflammation status that is currently considered a central biological mainstay of the aging process (Franceschi, 2007). Inflammaging is a condition induced by the senescence-associated secretory phenotype (SASP), which is produced by the innate immune, parenchymal, and nonparenchymal cells within the organs (Shirasuna and Iwata, 2017). Importantly, once cells become senescent, they produce and secrete the so-called SASP. SASP is thought to be the main driver of age-related inflammation (Franceschi, 2007). Broadly, SASP is composed of pro-inflammatory cytokines and chemokines, growth factors, proteases, and angiogenic factors that can act in a paracrine and autocrine manner to spread and strengthen senescence (Lopes-Paciencia et al., 2019). The presence of SASP-producing senescent cells can have negative long-term effects; such as chronic inflammation, that can produce tissue dysfunction and/or carcinogenesis (Rubio-Tomás et al., 2021).

Several theories have been postulated to explain the etiology of OvCa. Notably, these theories are likely not mutually exclusive, as they all converge on the role of inflammaging in promoting ovarian tumorigenesis and cancer progression.

We briefly discuss how each of these processes evokes or involves a persistent inflammatory response. This response leads to an environment rich in cytokines and growth factors in the internal genitalia and peritoneum and contributes to OvCa initiation, progression, and metastasis.

## 2. Inflammaging hypotheses of ovarian cancer (Fig. 1)

The most important hypothesis regarding OvCa carcinogenesis is the **ovulation theory**, which relates the risk of OvCa to incessant ovulation (Fathalla, 1971) and the etiological role of the inflammation that accompanies each ovulation (Huang et al., 2020). The tissue adjacent to the site of ovulation may be continually exposed to an inflammatory and oxidative environment; resulting in an increased risk of malignant transformation. Intriguingly, the ovulatory process and the repair steps following liberation of the ovum are characterized by the generation of an enormous amount of cytokines/chemokines and matrix-remodeling enzymes, including prostaglandins, bioactive eicosanoids, plasminogen activators, collagenases, ILs, TNF- $\alpha$  and various growth factors. It is also characterized by the recruitment of activated immune cells to the wounded epithelial surface, which represents the global activation of the proinflammatory network (Macciò and Madeddu, 2012).

Menstruation allows for **retrograde menstruation** and the possibility of ectopic implantation of endometrial tissue (Critchley et al., 2020). The risk of OvCa, particularly nonserous types, decreases after the retrograde route is blocked by tubal ligation (Pérez-López et al., 2017). The menstruating endometrium is rich in cytokines and prostaglandins. Iron metabolites in menstrual blood exposed to the fallopian tube epithelium (FTE) and ovary may exert the Fenton reaction upon iron oxides by interacting with the H<sub>2</sub>O<sub>2</sub> released from ovulation (Rockfield et al., 2019; Shigeta et al., 2016). Fenton reaction is an advanced oxidation process in which highly reactive hydroxyl radicals are produced. This is done under acidic environment conditions, with ambient pressure and temperature, using hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) that is catalyzed with transition metals, generally iron (Shigeta et al., 2016). Thus, ovulation and retrograde menstruation produce a repeated tolerable Fenton reaction in FTE and OSE, which can promote the development of OvCa (Rockfield et al., 2019; Shigeta et al., 2016).

The **gonadotropin stimulation hypothesis** proposes that high gonadotropin levels can influence OSE cells and promote carcinogenesis (Mertens-Walker et al., 2012) by increasing the proliferation and mitotic activity of the ovarian epithelium (Han et al., 2021). This fact could

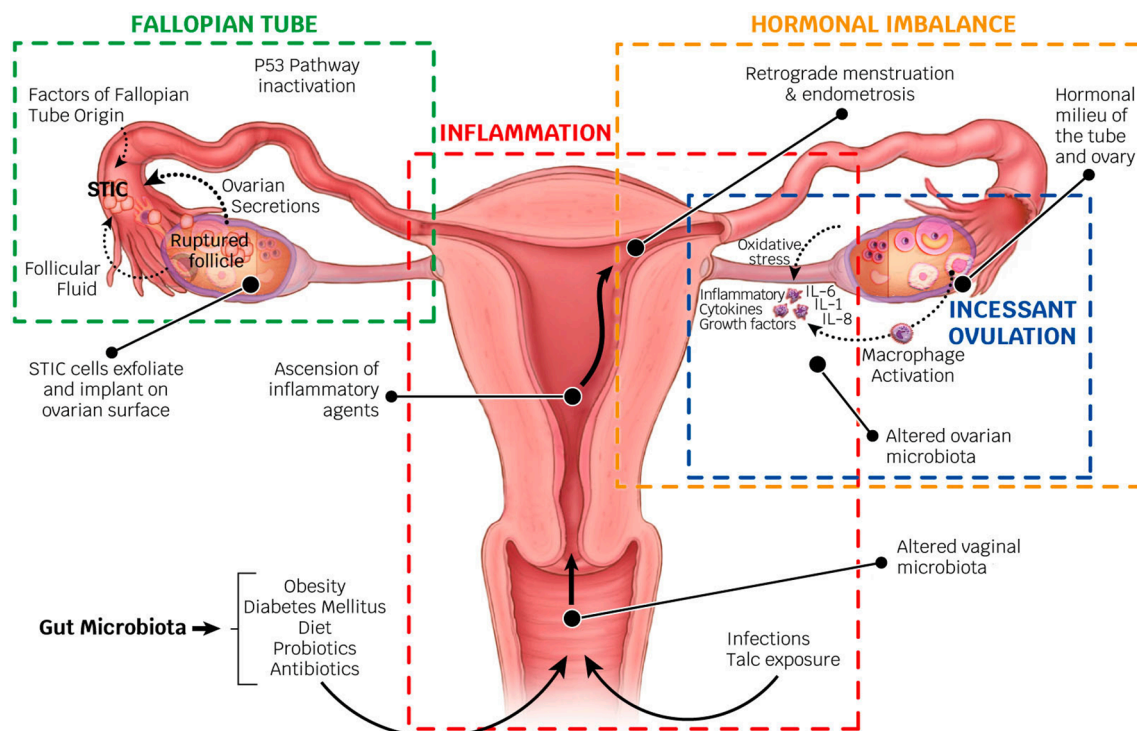


Fig. 1. Inflammaging hypotheses of ovarian cancer. Abbreviations: STIC, serous tubal intraepithelial carcinoma; ILs, interleukins.

explain why the majority of patients present with OvCa after menopause (American Cancer Society). The damage associated with the rupture of follicles during ovulation resulting from high levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estrogen are also risk factors and may lead to OvCa (Mertens-Walker et al., 2012). **Progesterone** plays a protective role in follicular fluid during pregnancy or exogenously (Wu et al., 2020). A cleansing effect of progesterone has been confirmed specifically on p53-defective tubal epithelial cells and on the progesterone receptor (PR) by inducing necroptosis, which is an inflammatory cell death that contributes to innate immunity (Wu et al., 2020). Therefore, endogenous or exogenous progesterone protects against carcinogenesis induced by ovulation and retrograde menstruation (Wu et al., 2020; Wheeler et al., 2019).

The fallopian tube, particularly the fimbriae, has emerged as another possible site of origin according to findings related to prophylactic surgery for reducing the risk of OvCa in women with a genetic predisposition to the disease (Hanley et al., 2022). Based on these observations, the **tubal inflammation hypothesis** was proposed by Salvador (Salvador et al., 2009). High-grade serous carcinoma (HGSC) and clear cell and endometrioid cancers have been hypothesized to arise from the epithelium of the fallopian tubes (Kurman and IeM, 2010) and share a common pathogenetic mechanism (Zhang et al., 2019), i.e., iron-induced oxidative stress derived from retrograde menstruation. The fallopian tube is regularly exposed to a variety of inflammatory agents and can show signs of acute and chronic inflammation. This inflammation is activated by constituents of the ovulatory follicular fluid (Hsu et al., 2019) and through the process of retrograde bleeding from the endometrial cavity during menstruation. Fimbriae floating in bloody peritoneal fluid is exposed to the action of catalytic iron and to the genotoxic effect of ROS generated from the hemolysis of erythrocytes by activated pelvic macrophages and by secreting cytokines (Macciò and Madeddu, 2012).

Emerging and, for some cancers, strong experimental and translational data support the contribution of the **microbiome** to cancer biology and disease progression (Knippel et al., 2021). The emergence of high-throughput technologies, such as genomics and transcriptomics, has afforded the generation of large volumes of data in relation to specific pathologies, such as different cancer types (Wei et al., 2021). A link has been demonstrated between alterations in the composition of the microbiota (**oncobiosis**, when referring to dysbiosis in neoplastic diseases) and the development of gynecological cancer (Borella et al., 2021). In OvCa, oncobiosis has been identified in numerous compartments, including the upper and lower female genital tract, serum, peritoneum, and intestines, as well as tumor tissue itself (Borella et al., 2021). Local inflammation probably participates in the initiation and continuation of carcinogenesis (Cheng et al., 2020).

Infection also induces inflammation in the fallopian tube (Salvador et al., 2009). Vaginal infections (for example, *Neisseria gonorrhoeae* or *Chlamydia trachomatis*) increase the risk of developing OvCa (Idahl et al., 2020). PID's are also associated with an increased ovarian cancer risk, as indicated by an updated meta-analysis (Piao et al., 2020). The role of viruses, such as human papillomavirus, in the initiation, promotion, and progression of OvCa is unknown (Ibragimova et al., 2021). With the use of highly sensitive techniques, several groups have detected the presence of a viral genome in OvCa tissues (Pathak et al., 2020), but it is not sufficient to prove that viruses are a causal factor in the genesis of the disease (Cherif et al., 2021).

Another example of an inflammatory factor involved in the carcinogenesis of OvCa is the use of talcum powder in the genital area. Talc, along with associated components such as asbestos or quartz, which are known carcinogens and can contaminate talc products, might ascend through the genital tract and irritate the epithelial lining of the fallopian tubes or ovaries. This could possibly trigger an inflammatory response that may promote carcinogenesis. Taken together, epidemiological data suggest that there may be a small positive association between the use of genital powder and OvCa (Wentzensen and O'Brien, 2021).

The **tumor microenvironment** (TME) is composed of a variety of immune cells and stromal cells and is crucial in the occurrence and development of OvCa (Shan and Liu, 2009). Oncogenic RAS-transformed ovarian epithelial cells generate a proinflammatory secretome that diffuses into the stroma and causes fibroblast senescence. Senescence of ovarian stromal fibroblasts creates a secondary proinflammatory phenotype and converts the ovarian epithelial microenvironment into a field filled with inflammatory mediators that advance tumor progression. The inflammatory network contributes to the communication between the ovarian tumor epithelium and the underlying stroma (Shan and Liu, 2009).

### 3. Other potential origins (Fig. 1)

Metabolic disorders, such as diabetes, dyslipidemia, hypertension and obesity, have been determined to overactivate the immune system by causing leukocyte activation. An increase in the number of leukocytes is associated with proinflammatory phenotypes and thus explains the predisposition to chronic inflammatory diseases (Garn et al., 2016). Oxidative stress mediated by toxic habits (such as smoking), excessive pollution, allergies, sleep disorders and increasing age has also been demonstrated to predispose patients to a chronic inflammatory state (Garn et al., 2016).

**Metaflammation** (the metabolic inflammation that accompanies metabolic diseases) is believed to be a form of chronic inflammation that is driven by an excess of nutrients (Franceschi et al., 2018). Consequently, nutrition influences the incidence, natural progression and therapeutic response of malignant diseases by modulating chronic inflammation (Zitvogel et al., 2017).

**Obesity** is associated with a higher incidence of and poorer survival in OvCa (Craig et al., 2016). A positive association has been found between the **dietary inflammatory potential** measured by the *Dietary Inflammatory Index* (DII) and the OvCa, and there is a significantly higher risk of OvCa in postmenopausal women (Yang et al., 2022). Most of the recent studies on epithelial OvCa have suggested a relationship between increasing body mass index (BMI) and nonserous histologies (Wichmann and Cuello, 2021). Additionally, obesity increases the risk of serous histologies that arise from the peritoneum (Wichmann and Cuello, 2021).

It has been proven that adipose tissue not only serves as calorie storage but also as a source of both proinflammatory and anti-inflammatory factors, known as adipocytokines (Craig et al., 2016). **Adipocytes** promote OvCa epithelial growth, invasion, metastasis, and angiogenesis through adipokine secretion, metabolic remodeling, and modulation of the immune microenvironment (Dai et al., 2020). Therefore, it has been suggested that organs rich in adipocytes, such as the omentum, may be sites of both metastasis and origin. That is, they may serve as a site of the initial seeding and transformation of malignant precursor cells that originate in other parts of the abdomen (Iyoshi et al., 2021). This could explain why apparently cancer-free women are diagnosed with advanced-stage disease within a few months.

Studies have shown a strong correlation between **diabetes mellitus** (DM) and carcinogenesis, and the most evident correlation that has been reported is between carcinogenesis and type 2 diabetes mellitus (T2DM). T2DM has been reported to cause T cell senescence in both prediabetic and diabetic patients (Broadway et al., 2021). Hyperglycemia causes epigenetic alterations through several mechanisms; including DNA methylation and chromatin remodeling, and results in abnormal gene expression. A systematic review and meta-analysis evaluated the association between DM and the incidence of OvCa and suggested that women with DM had a 20% elevated risk of OvCa compared with those without a history of DM (Wang et al., 2020).

### 4. Discussion

OvCa is a multifactorial disease, including demographic,



reproductive, gynecologic, hormonal, genetic, and lifestyle factors (Tanha et al., 2021).

Ovulation has a significant contribution to the etiology of OvCa. However, the peak incidence of OvCa occurs at approximately 63 years of age, which is more than a decade after the mean age of menopause (Gibson et al., 2016). Following depletion of the ovarian follicles, the remaining ovary is reduced to collagen scar tissue (Jia et al., 2018). The migration of malignant cells from the oviduct to the ovary via a cytokine/chemokine gradient formed from the surface of the wounded ovary could potentially explain why menopausal women are at a higher risk of OvCa (Pakuła et al., 2020). This phenomenon might also explain the protective effect of hysterectomy, salpingectomy, and tubal ligation against the development of OvCa (Pérez-López et al., 2017).

Several other factors, such as senescent cells, are involved in age-related increases in carcinogenesis (Pakuła et al., 2020), but inflammation is one of the most prominent factors. In fact, inflammation is characterized by the establishment of a systemic proinflammatory state with increased levels of circulating interleukins, such as IL-6, IL-1 and TNF- $\alpha$ , and inflammatory markers, such as C-reactive protein (CRP) (Leonardi et al., 2018). These factors have been shown to be associated with the risk of OvCa (Peres et al., 2019). This results from the activation of signaling networks critical to inflammation, along with a variety of different sources of the inflammatory stimuli triggering and sustaining inflammation. Such sources include those that occur in the external genitalia (bacterial and viral infections, changes in the vulvovaginal microbiome, exposure to external toxins, etc.) and, above all, in the internal genitalia (ovulation, endometriosis, PID). However, they can also occur from extragenital causes, such as meta-inflammation (Craig et al., 2016), the gut microbiota (Rubio-Tomás et al., 2021), and nutrition (Yang et al., 2022).

Unlike most other tumor types that metastasize via the vasculature, OvCa metastasizes predominantly via the transcoelomic route within the peritoneal cavity. Selectins are glycan-binding molecules that facilitate the initiation of tumor-mesothelial adhesion in the peritoneal cavity, and the important role of selectins in peritoneal carcinomatosis of OvCa has emerged (Hassan et al., 2020). Their role in inflammation is recognized, expressing P- and E-selectins at sites of inflammation (Hassan et al., 2020).

Discovering which cellular and molecular processes promote and inhibit the seeding of malignant cells to the ovary could facilitate the development of markers for early detection as well as the identification of rate-limiting events in the early stages of OvCa development, when cures are more viable (Kotsopoulos et al., 2016).

In conclusion, this narrative review adds to the existing evidence that inflammation and inflammatory mediators play a role in ovarian carcinogenesis. However, we need to better understand the mechanisms by which the inflammaging process culminates in ovarian tumor initiation, as it does in other tumors. Thus, we can develop ways to target inflammatory mediators and reduce the risk of OvCa.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Glossary

CA125: Cancer antigen 125  
CRP: C-reactive protein  
DII: Dietary inflammatory index  
DM: Diabetes mellitus  
DNA: deoxyribonucleic acid  
FTE: Fallopian-tube-epithelium  
FSH: Follicle stimulating hormone  
HPV: Human papillomavirus  
IIE: Impaired inflammatory state of the endometrium  
IL: Interleukin  
LH: Luteinizing hormone  
NF- $\kappa$ B: Nuclear factor- $\kappa$ B  
OSE: Ovarian surface epithelium  
OvCa: Ovarian cancer  
PID: Pelvic inflammatory disease  
PR: Progesterone receptor  
ROS: Reactive oxygen species  
SASP: Senescence-associated secretory phenotype  
T2DM: Type 2 diabetes mellitus  
TME: Tumor microenvironment  
TNF: Tumor necrosis factor  
Tregs: Regulatory T cells